**Universidade de Lisboa**

**Faculdade de Farmácia**

# Innovative Therapeutic Approaches to Fight Glioblastoma

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**Mestrado Integrado em Ciências Farmacêuticas**

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# Abstract

Glioblastoma is an aggressive tumour of the central nervous system, with limited survival and poor treatment options. The standard therapy consists of surgical resection followed by radiation therapy and chemotherapy with Temozolomide (TMZ). Patients with glioblastoma have a low life expectancy and even after treatment, recurrence is almost certain. Research its being made to find new therapies that can improve the standard treatment and prognosis.

With the advances of science, the pioneering therapies comprise targeted therapies, immunotherapy, virotherapy, gene therapy, among others. Targeted therapies consider the many pathways that tumour uses to grow and survive, such as receptor tyrosine kinase/phosphoinositide 3-kinasen/mitogen-activated protein Kinase (RTK/PI3K/MAPK) pathway, p53 and retinoblastoma protein (pRb) pathways, and other important signalling transduction pathways, such as polyamine biosynthetic pathway. With the knowledge of which proteins and genes contribute to the proliferation of the tumour, that information can be used to target the cancer cells and restrain the glioblastoma growth. The immunotherapy uses the immune system of the patient as a pathway to fight the tumour and includes CAR-T cells therapy, TIL therapy, TCR therapy, vaccination and immune checkpoint inhibition. The virotherapy uses the oncolytic activity of the virus to target the tumour cells and destroy them. Gene therapy inserts, modifies or inactivates a gene in order to fight the disease. Additionally, there are other different therapies being investigated, that consider other mechanisms, such as the cholesterol metabolism and hyperthermia.

Since glioblastoma is a fatal disease, more options for treatment are needed to improve quality of life and the overall survival of the patients. The purpose of this dissertation is to analyse the future of glioblastoma treatments, looking to the innovative therapeutic approaches that are under development Although these new therapies, look promising to assemble a new treatment, issues related to the tumour itself, to the central nervous system and to clinical trials design are a huge challenge that will be further discussed.

**Keywords**: Glioblastoma; Novel therapeutics; Targeted Therapies; Immunotherapy; Virotherapy

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# Introduction

Glioblastoma is the most aggressive and common tumour of the central nervous system (CNS), having a fast-growing and invasiveness that leads to a high morbidity and mortality (1,2).

Considering it is an heterogenous brain tumour, with fast-development, recurrence is usual and inevitable. The tumour exhibits significant resistance to the therapy and, treatment options for recurrent disease are rather limited (3,4).

## Classification of Glioblastomas

The term 'glioblastoma multiforme' (GBM) was introduced in 1926 by Cushing and Bailey to describe the heterogeneity found on the histologic examination of glioblastoma cells. (2,5) This classification was replaced by the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (2,6).

Nowadays, and according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System, glioblastomas are classified as IV grade diffuse astrocytic and oligodendroglial tumours (7,8). This classification divides CNS tumours following the genotypic and phenotypic features. Hence, glioblastomas can be divided in three vast groups, according to the existence or inexistence of mutations in isocitrate dehydrogenase (IDH): glioblastoma IDH-wildtype, glioblastoma IDH-mutant and Glioblastoma, Not wised specified (NOS), as showed in figure 1(7).

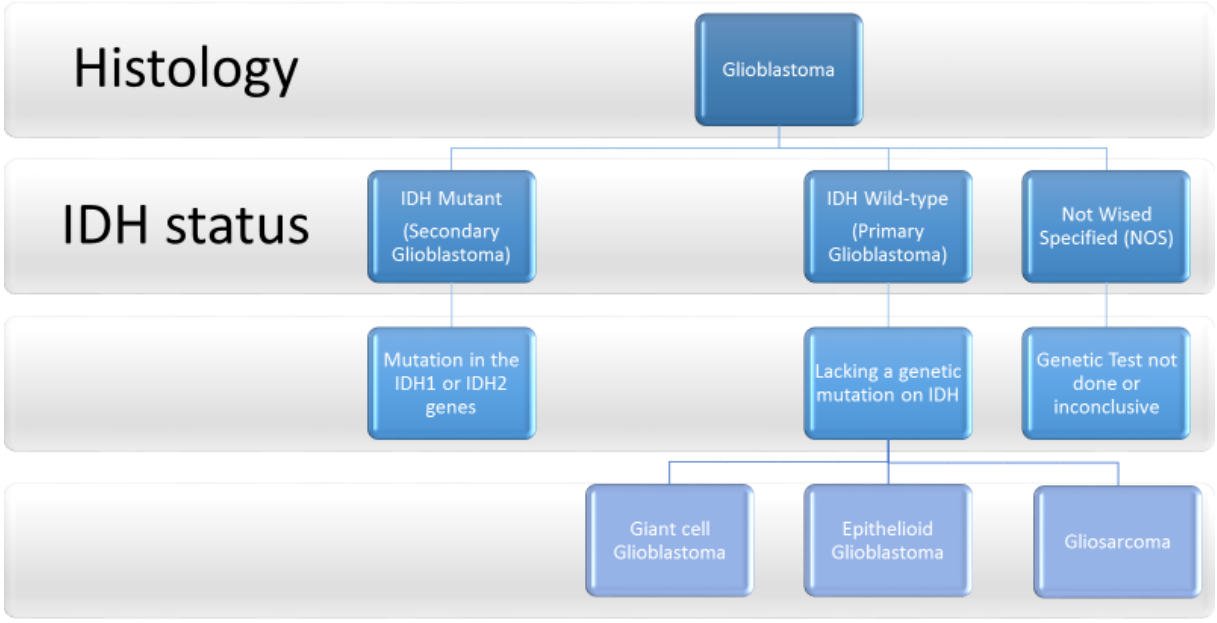


*Figure 1* – Algorithm, based in the 2016 World Health Organization Classification of Tumours of the Central Nervous System, to systematise the different types of Glioblastomas.

Adapted from Louis DN, Perry A, Reifenberger Guido, Von Deimling A, Figarella-Branger D, Webster·, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol, (7).

Glioblastoma IDH-wildtype is the most common type (approximately 90% of cases), affecting older patients (media of ages is 62 years). It is defined as primary glioblastoma or de *novo* glioblastoma due to its rapid progression from non-neoplastic brain cells without a precursor lesion. Usually, it is in the supratentorial region and is defined by the extensive necrosis and the existence of mutation in the Telomerase Reverse Transcriptase (TERT) promoter in 72% of cases. The median overall survival (OS) with the gold-standard of therapy is 15 months. In this group, we can also add gliosarcoma, epithelioid glioblastoma and giant cell glioblastoma, with a similar molecular profile but a different morphology (7–9).

Glioblastoma IDH-mutant (about 10% of cases), corresponds to the secondary glioblastoma, developing from a prior lower grade diffuse glioma. It affects younger patients (media of ages is 44 years) and is located preferentially in the frontal region. It has a limited necrosis, having TP53 and alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutations in 81% and 71% of cases, respectively. The OS with the standard treatment is 31 months, having a better prognosis than Glioblastoma IDH-wildtype (7–9).

Glioblastoma NOS corresponds to the glioblastomas in which the IDH classification is not possible, either because the test is not done or because is inconclusive (7,9). This means that the diagnosis is made based only on histologic features (9).

The different mutations present in glioblastomas are considered diagnostic biomarkers and help differentiate the tumours, giving more information that can be used to identify the best treatment option (9). Nowadays, there are several new biomarkers, but the ones that are commonly used in a daily routine are: IDH (prognostic value, referred to previously), O-6-methylguanine-DNA methyltransferase (MGMT), and 1p/19q co-deletion (predictive) (1). We can divide patients with glioblastoma concerning the presence or absence of the methylation in the promoter of O-6-methylguanine-DNA methyltransferase (MGMT) gene, which encodes a protein that repairs DNA damages. This promoter methylation is connected with a low activity on repairing DNA giving a better prognosis with the current chemotherapy treatment – Temozolomide (TMZ) (3,10).

## Gliomagenesis

Although many studies have been done and new biomarkers, gene mutations have been found, the exact mechanism of gliomagenesis is uncertain. It is thought that the cellular origin is from primitive pluripotent cells, including neural stem cells, glial precursor cells, and oligodendrocyte precursor cells (2). There is also a consensus that GBM incorporates cancer stem cells (CSCs), cancer-initiating cells, and cancer-propagating cells that have the ability of self-renewal and tumor initiation that leads, briefly, to the development of a new tumour, resulting in resistance to the current therapy (11,12). It is assumed that the gliomagenesis is a phased process, involving different potential genetic changes (13).

The Cancer Genome Atlas (TCGA) has identified some pathways that are disrupted and that have been linked to the development of glioblastoma: receptor tyrosine kinase/phosphoinositide 3-kinase/mitogen-activated protein kinase (RTK/PI3K/MAPK) (almost 90% of the cases), p53 (86% of the tumours) and retinoblastoma protein (pRb) (79%) pathways. The RTKs when activated stimulates the PI3K pathway that controls cellular events. The p53 and RB genes are typical tumour suppressor genes that inactivate mutations in the cell cycle (G1 to S phase). This genetic and molecular identification allowed for an additional classification of glioblastoma,in 4 subtypes: classical GBM, mesenchymal GBM, proneural GBM and neural GBM. (14–16).

Although some of the mechanisms that lead to gliomagenesis are known, there is no specific cause for the development of glioblastoma, for most patients. Researchers have studied many possible risk factors such as environmental and behavioural but there is no minimal evidence of association to GBM, therefore it is impossible to decrease the incidence as done for other types of tumours (1,17). The only cause recognised as GBM risk factor is exposure to radiation. This is only for a minority of the patients with GBM, being other possible causes, the genetic predisposition to tumorigenesis (leading to different tumours including GBM) or also a strong family history of cancer (1,17,18). On other hand, there is a reduced glioblastoma risk for those who have allergies, autoimmune diseases, reported history of varicella-zoster virus (VZV) infections or the presence of Immunoglobulin G (IgG) to VZV (17).

## Angiogenesis

Angiogenesis is a key process in the development and survival of tumours being the adequate blood supply a known feature. In the case of Glioblastoma it is extremely vascularized (19,20).

The establishment of these complex blood vessels is coordinated by several angiogenic factors, such as, Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF) and Platelet-Derived Growth Factor (PDGF) (19).

## Clinical Presentation

The clinical presentation of glioblastoma is connected to the area of the brain that is affected, but also with the size and rate of growth of the GBM. Usually, the symptoms are presented when the tumour is in an advance state and they can be confused with other diseases. These symptoms are subtle and include headaches, fatigue, neurologic deficits. Seizures can also occur in some patients (1,18,19).

## Development of Novel Therapies for GBM – Challenges

Developing new therapies for GBM is a challenge since CNS and GBM itself are complex structures. Many obstacles can be pointed out as the cause of failure of new therapies and many obstacles remain unknown (18).

There can be some potential barriers in the developing stages of the potential treatments. The preclinical models are not representative of GBM and it is impossible to collect all the needed information from them (1,18). Therefore, there is the need of better models and there is the necessity to optimize the clinical protocols and to create clinical trials that estimate the effectiveness of the therapy instead of overestimating the probability of success that leads to late-stage failure (18,21,22).

Other potential barriers are connected to the characteristics of the CNS and Glioblastoma.

Glioblastoma is characterized as an heterogenous tumour, with many deregulated pathways that lead to therapy resistance. One challenge is the difficulty to cure GBM with a single therapy, since GBM has many targets, and many resistant mechanisms (1,11). Secondly, the GBM has abnormal vessels and areas of necrosis that prevent a good distribution of the medicine (18). Also, the brain impairs drug delivery by having a physic and metabolic barrier ,the Blood Brain Barrier (BBB), that can prevent the entrance of the medicine or efficiently pump the medicine out, through the efflux pumps (18,21,23).The drug delivery is a challenge. When assessing a new therapy, it is required to look at the characteristics of the medicine: it should be permeable to the BBB (having the right lipophilicity and size) and they should reach a therapeutic concentration even if distribution is not homogeneous (21).

# Glioblastoma Current Treatment Options

The current standard of treatment involves maximal surgical resection followed by radiation therapy and concomitant Temozolomide (TMZ), with subsequent adjuvant chemotherapy with TMZ for 6 to 12 months, for patients with ages lower than 70 years (3,4,18,24,25). The maintenance therapy can also be combined with Tumor Treating Fields (TTF's) (24,26).

The prognosis of the treatment is dependent on the type of glioblastoma, as referred previously.

The treatment options for recurrence are more restricted and involve the use of chemotherapeutic agents (mostly, nitrosoureas) and monoclonal antibodies such as bevacizumab (not approved in Europe), an inhibitor of vascular endothelial growth factor (VEGF), important in tumour angiogenesis (26). Since there is an absence of a specific guideline to advise the best therapy, treatment options are made based on numerous factors, namely: age, tumour extent and site, preceding therapies and the length of the disease. Even treating recurrent glioblastoma, the median overall survival is 6.2 months, being the longest OS achieved of 12 months, with bevacizumab plus lomustine (alkylating nitrosourea). (21)

## Surgery

Surgery is the initial treatment. It is also a diagnostic tool, as it enables a molecular diagnosis (1,2).

The retrospective data shows that the surgery has a better outcome if the resection is performed to the safe highest extent (1,18). Although, due to the infiltrative nature of this type of tumour, the complete resection is not a sign that the disease is cured, as the GBM cells can remain and form a new tumour (1,2).

Considering the limitations of the current surgical methods, many new procedures are under development (1). *Table 1* exposes some of the new elaborated practises of the surgical field.

## Radiotherapy (Radiation Therapy)

Radiotherapy plays a key role in the treatment of glioblastoma as it is an effective treatment shown to improve survival. The standard dose is 60 Gy in 30 fractions, 3 or 4 weeks after the surgery, being the duration of the treatment 6 weeks (2,3,18). Patients with characteristics that point to a worst diagnosis such as more than 70 years old, are generally treated with hypo fractioned radiation (dose of 40 Gy administered in 15 fractions) (25). With these schemes of therapy, the cancer cells are killed considering that the radiation stops the cell cycle and induces apoptosis (3).

Since radiotherapy is one important tool in glioblastoma therapy, there are different new techniques being established. *Table 1* displays the different radiotherapy methods being explored.

## Chemotherapy

Chemotherapy uses the alkylation agent TMZ, that breaks DNA double-strand and decreases the activity of MGMT (DNA repair enzyme), stimulating cell cycle arrest and cell death (1,27). This is the first-line therapy drug in combination with radiotherapy (3). In a Phase III clinical

*Table 1* – Innovations and new techniques within glioblastoma therapy to improve the outcome, focusing in 3 fields: Surgery, Radiotherapy, Chemotherapy. Adapted from Alphandéry E. Glioblastoma Treatments: An Account of Recent Industrial Developments. Front Pharmacol .2018 ;9:879 (1)

| | | | |
|---|---|---|---|
| SURGERY | Methods used for maintaining patients awake during surgery | Awake craniotomy (AC) | |
| | | Surgical Robot | |
| | Imaging Thechniques used during surgery | Fluorescent Imaging Systems | Positron Emission Tomography (PET) |
| | | | Confocal Laser Endo-microscope (CLEM) |
| | | | Optical Coherence Tomography (OCT) |
| | | Magnetic Imaging Systems | Intraoperative magnetic resonance imaging (iMRI) |
| | | | Functional Magnetic Resonance Imaging (fMRI) |
| | | | Magnetoencephalography (MEG) |
| | | | Navigated transcranial magnetic stimulation (nTMS) |
| | | Other Imaging systems | Diffusion tensor imaging fiber tracking (DTI-FT) |
| | | | Intraoperative mass spectometry (MS) |
| RADIOTHERAPY | External Beam radiation therapy (EBRT) | Three dimensional conformational radiation therapy (3D-RT) | |
| | | Intensity modulated radiation therapy (IMRT) | |
| | | Helical-tomography (HT) | |
| | | Stereotactic radiosurgery (SRT) | |
| | | Gamma Knife | |
| | | Cyber Knife | |
| | | Proton radiation therapy (PRT) | |
| | Internal radiation therapy (IRT) or brachytherapy (BT) | Gliasite | |
| | | Radioactive monoclonal antibodies | Cotara |
| | | Radiosensitizer | KU-60019 |
| CHEMOTHERAPY | Drug Formulations | Transferrin-bearing therapeutic | |
| | | Thermosensitive liposomes | |
| | | Angiopep-2 and anti-CD133 | |
| | Convection-Enhanced Delivery (CED) | | |
| | Modification of BBB | Intra-Arterial Chemotherapy | |

trial, using TMZ plus radiotherapy, followed by adjuvant TMZ for 6 months, the results have shown that the overall survival improved when comparing to radiotherapy alone. Even when a trial was conducted in an elderly population, the results were as positive, leading to a longer survival (28,29). TMZ is used at a daily dose of 150-200mg/$m^2$ of body surface-area (BSA) for 5 days every 28-day cycle (1).

As mentioned before, there is the possibility of resistance to TMZ when there is a demethylation from O6 position of guanine by O6-methylguanine methyltransferase (MGMT) (27). Hence, the patients that have a methylated MGMT and supressed MGMT expression, benefit with chemotherapy with TMZ, having a better prognosis and an improved 2-year survival (1,27,30).

Considering that one of the biggest challenges in glioblastoma therapy is drug delivery of chemotherapeutic agents, in *table 1* there are some innovative techniques to help outcome this issue.

## Tumour Treating Fields (TTFs)

TTFields are a non-invasive treatment for glioblastoma They are mild electric fields with low-intensity (>0.7–3 V/cm) and intermediate frequency (100-300 kHz) that pulses through the skin of the scalp of patients to disrupt mitosis in cancer cells (4,31). They are used for at least 18 hours per day, as it is proven that helps achieve a longer median overall survival (18,31).

TTFields can be described as having an antimitotic effect as they interfere with the normal polymerization of microtubules in metaphase, and cell destruction by giving the septin complex (polar particles) a non-uniform electric field (dielectrophoresis), in the end of telophase and beginning of cytokinesis (24,31,32). The TTFields have an inhibitory effect only on proliferating cells (32) and can be used in a variety of tumour cell lines and in animal models (4).

Following the results of the studies effectuated (phase III clinical trial Ef-11 and phase III clinical trial Ef-14), TTFields can be used in recurrent glioblastoma and in newly diagnosed glioblastoma. The results showed that the treatment with TTFields is similar to a physician's choice chemotherapy being the benefit of using TTFs the superior safety and quality of life, as TTFields show a lower profile of toxic effects. On the other hand, the limiting element of this novel therapy can be the low compliance of the patient concerning the nature of the device (18,24,31,32).

The randomized trial EF-14 showed also, that the addition of TTFields with the adjuvant chemotherapy, increases the overall survival and prolongs the progression free of cancer cells, constituting a "fourth cancer treatment modality" (4,24).

### Recurrent Setting

## Nitrosoureas

Nitrosoureas are alkylating agents, which cause DNA damage and cellular death. They are important chemotherapeutic agents used since the 1970's to treat glioblastoma, being the most used ones: lormustine, carmustine and fotemustine. However, due to a toxic profile and the introduction of temozolomide and other therapeutic agents for newly diagnosed glioblastoma, nitrosoureas are second-line treatment. (33)

- ***Gliadel wafers***

Gliadel wafers are an alternative to TMZ and consist of biodegradable polymers containing carmustine, also known as BCNU (bis (bis-chloroethyl nitrosourea). The wafers are implanted

in the resection cavity during surgery, providing the therapeutic dose on-site (22,27). Studies have been made, and the results of the phase III clinical trial have revealed an improvement of the median survival to 21 months, when combining the gliadel wafers with concomitant TMZ (1,27,34,35). However, it has been demonstrated that there are toxic effects associated. There is the need to develop more clinical trials, and maybe design a better structure of the wafers to prevent toxic effects (34–36).

- ***Lomustine (CCNU)***

Lomustine is another alkylating agent used to treat GBM. It is administered orally at a dose of 90 to 110 mg/mq. When comparing to BCNU, lomustine is preferable considering it has a better toxic profile and regarding its oral formulation. (33)

As mentioned before, the combination of lomustine and bevacizumab is being studied as treatment for the recurrent glioblastoma. Although results from the phase II trial seemed promising with an OS of 12 months, the phase III trial showed that the results achieved with this combination (OS of 9.7 months) are equivalent to the results when using lomustine alone (OS of 8.6 months). (37)

Highlighting this, the use of CCNU or the use of CCNU and bevacizumab is being considered as second-line treatment, after therapy failure with TMZ (33).

## Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody that targets vascular endothelial growth factor (VEGF) and has been approved for glioblastoma treatment, in recurrent setting, by the Food Drug Administration (FDA) in the USA, in 2009, being administered intra-venously at a dose of 10 mg/kg, every two weeks.(1,13).

Many clinical trials were conducted to investigate the efficacy of bevacizumab. The clinical trials were carried in patients with newly diagnosed glioblastoma, (38–42) with recurrent glioblastoma (43), with bevacizumab alone (44) or in combination with other agents: irinotecan (45,46), lormustine (47), TMZ (48). The results obtained demonstrated that bevacizumab is well tolerated, that it is possible to improve survival, although this has no statistical relevance, as it hasn't improved the overall survival (OS). Therefore, there are more clinical trials in progress, and there is still the need of more studies to determine the efficacy of bevacizumab (1,19,27).

# Innovative Therapeutic Approaches to Fight Glioblastoma

Considering that glioblastoma is the most devastating primary tumour of the CNS, there is an urge to develop new therapies. Nowadays, the innovative treatments that are under development concern targeted therapies due to the gained knowledge on molecular mechanisms of glioblastomas, immunotherapy virotherapy and cell/gene therapy

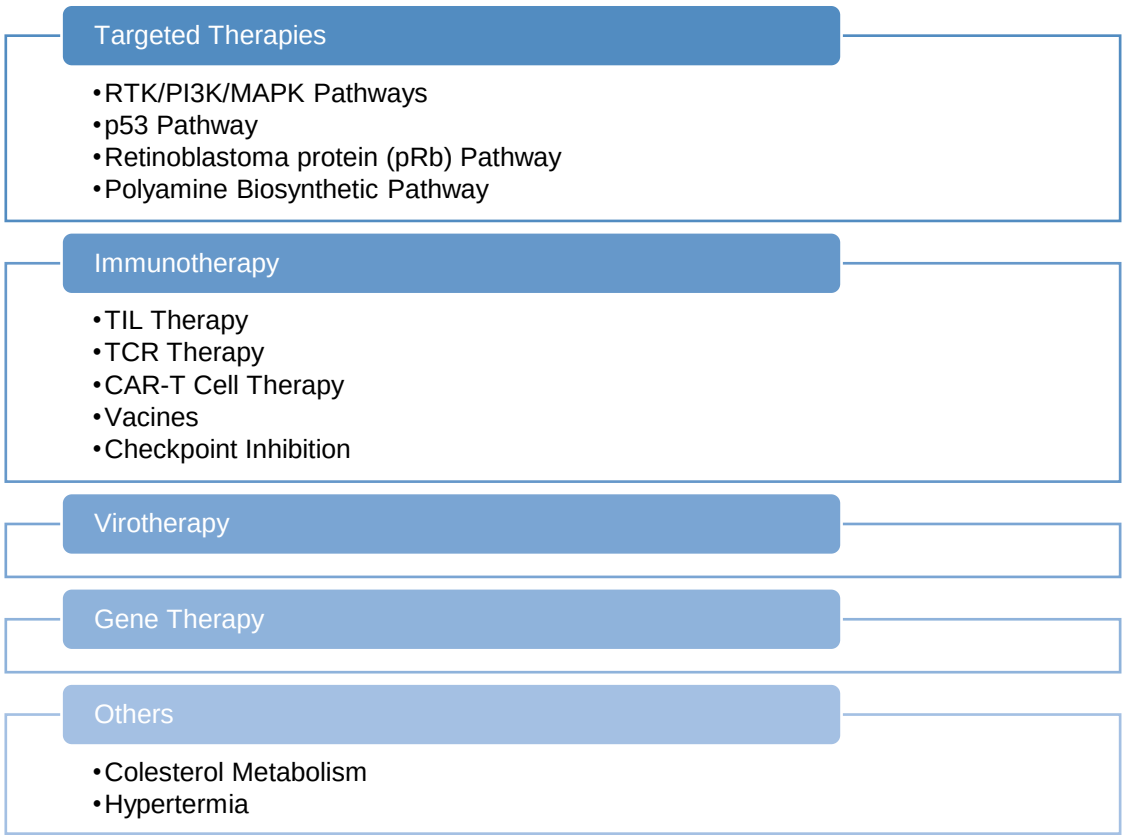


*Figure 2* – Summary of innovative therapeutics for Glioblastoma.

## Targeted Therapies

Targeted tumour therapy uses the knowledge about what contributes to the growth, survival and spread of the tumour, such as, proteins, genes, molecular pathways to hit the cancer cells stopping their growth and survival. Targeted tumour therapies may use a variety of substances in order to fight the tumour such as small molecules, small molecules drug conjugates, monoclonal antibodies, antibody-drug conjugates (ADCs).

- ***RTK/PI3K/MAPK Pathways***

These signalling pathways (RTK/PI3K/MAPK) play a key role in the cellular development, survival and differentiation. The pathways are activated by growth factors such as Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth

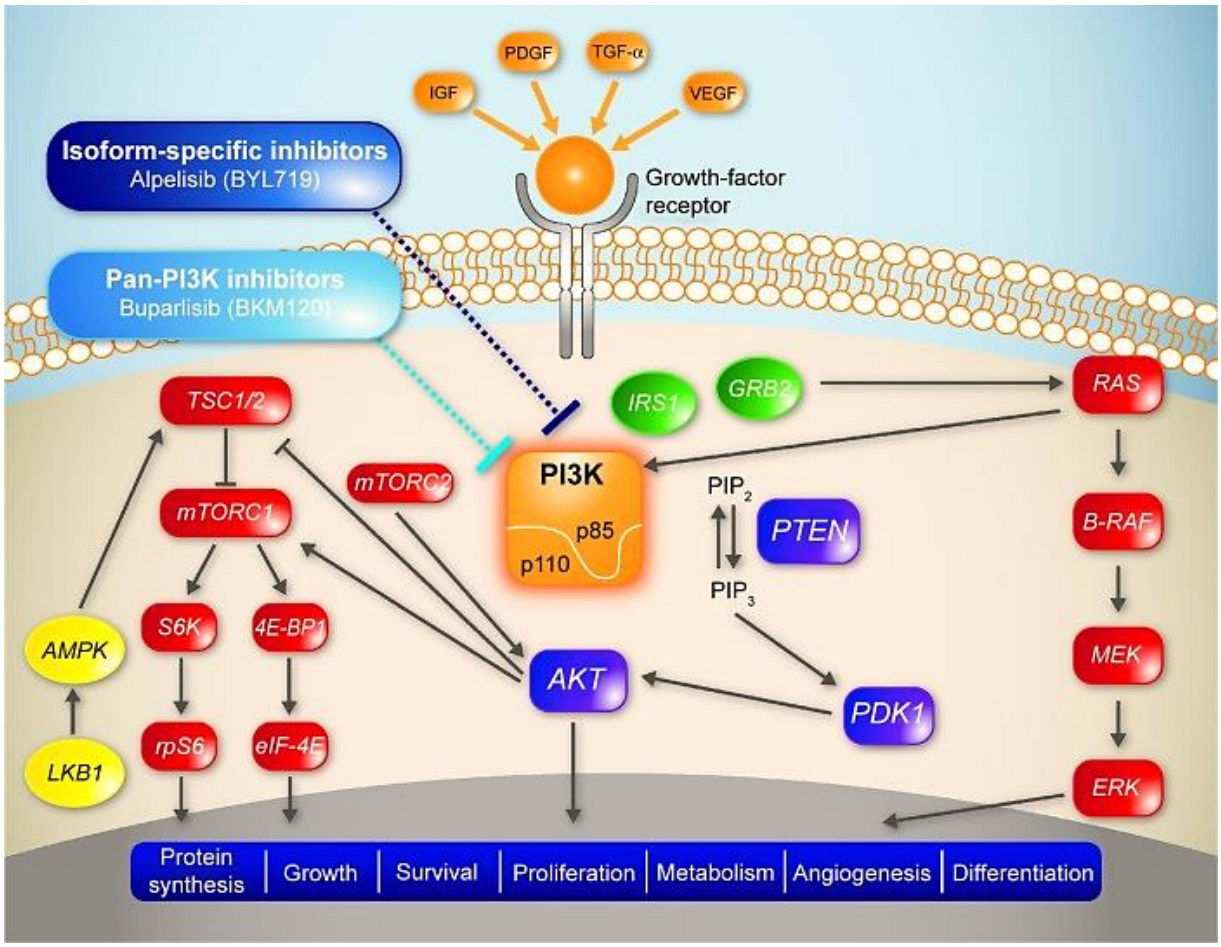


*Figure 3* – The RTK/PI3K/MAPK signalling pathways. The MAPK pathway: The growth factors such as IGF, PDFG, TGF-α, VEGF bind to the extracellular part of the respective receptor. This results in the dimerization of the receptor and the autophosphorylation of a tyrosine residue in the intracellular part. The GRB2 protein docks to the phosphorylated tyrosine residue, through its SH2 domain and gets activated. The GRB2 then recognizes SOS protein that binds to its SH3 domain. Together, these proteins identify inactive Ras, which is connected to GDP. SOS catalyses the activation of Ras through the phosphorylation of GDP into GTP. Active Ras can bind to several effector proteins such as B-Raf. When B-Raf gets activated, phosphorylates and activates MEK, which then phosphorylates and activates ERK that leads to the kinase cascade that conducts to the activation of transcription factors of the AP-1 family. AP-1 controls several cellular processes including differentiation, proliferation, and apoptosis The PI3K pathway: This pathway starts with the activation of PI3K. This can be achieved either by the binding of PIP3 to Ras or with the activation of the receptor belonging to RTK family, by an external growth factor. This leads to dimerization and heterologous phosphorylation of the monomer's constituents of the receptor. Different proteins may bind to the phosphorylated domain, such as IRS-1. After bonding, IRS-1-RTK becomes an active site for the PI3K, that can bind directly. In the second stage of this pathway, PI3K is activated and binds to PIP2. After phosphorylation, PIP3 is formed and can activate AKT, which is a proto-oncoprotein, with many substrates and effects. One of the effects is inhibition of apoptosis, made through the bonding of AKT to BAX. Another important effect is activation of protein synthesis. This is performed by a multi-step protein cascade. It begins with the activation of Rheb which activates mTOR, that, in its turn interacts with S6K. S6K binds to the large subunit of ribosomes and activates the translation of mRNA.



Abbreviations: **EGF** - Epidermal Growth Factor, **PDGF** - Platelet-Derived Growth Factor, **VEGF** - Vascular Endothelial Growth Factor, **TGF-α** - Transforming growth factor alpha, **GRB2** - Growth factor receptor-bound protein 2, **SOS** – Son of Sevenless, **GDP** - guanosine diphosphate, **GTP** - Guanosine-5'-triphosphate, **MEK** (also known as, MAPKK or MAP2K) -- Mitogen-activated protein kinase kinase, **ERK** (also known as MAPK) - Mitogen-activated protein kinase, **AP-1** - Activator protein 1, **PI3K** - Phosphoinositide 3-kinase, **RTK** - Receptor tyrosine kinase, **IRS-1** -- insulin receptor substrate 1, **PIP3** - Phosphatidylinositol (3,4,5)-trisphosphate, **PIP2** - Phosphatidylinositol 4,5-bisphosphate, **AKT** (also PKB) - Protein kinase B, **BAX** - bcl-2-like protein 4, **Rheb** - Ras homolog enriched in brain, **mTOR** - mammalian target of rapamycin

Factor (VEGF), Transforming growth factor alpha (TGF-α), that bind to its respective growth-factor receptor. In MAPK pathway, this causes the dimerization of the receptor and the autophosphorylation of a tyrosine residue in the intracellular part. This leads to a signal transduction cascade, that ultimately results in the activation of transcription factors, as shown in *figure 3*. In PI3K pathway, the docking of a protein into the receptor allows PI3K to be activated, binding to PIP2. PIP2 is phosphorylated into PIP3 and PIP3 can activate the proto-oncoprotein ATX, also shown in *figure 3*. This protein has many substrates that regulates several cellular processes (16,49).

These pathways can become dysregulated due to many reasons. In the MAPK pathway can be by activating mutations in Receptor tyrosine kinase (RTK) or Kras (gene that controls cell proliferation), or inactivating mutations in its negative regulator, NF1.In the PI3K pathway, it can be triggered by activation of the inhibitor of this signalling transduction pathway, Pten. These mutations can lead to a permanent activation of these pathways, leading to undesirable effects (16).

The RTK/PI3K/MAPK signalling pathway is modified in 90% of the patients with glioblastoma which contributes to the subsistence, increase and migration of the cancer cells (16).

Since this pathway is changed in most of GBM cases, it is one of the most appealing targets for GBM therapy (14). There are many molecules under evaluation.

**Sonolisib**, or **PX-866**, is an irreversible inhibitor of the PI3K pathway and it was studied in a phase II trial. The results were not promising, although there were 21% of the 33 participants, with a durable stable disease (14,26,50). **Buparlisib**, a pan-PI3K inhibitor, is also under development. A phase II trial has revealed clinical activity when in combination with bevacizumab, even though, alone shows restricted effectiveness (26,51,52).

The mammalian target of rapamycin (mTOR) is another possible target. **Everolimus**, **sirolimus**, **temsirolimus**, inhibitors of mTOR, are approved for treating other tumours, with significant clinical results. Now they are being studied as treatment for glioblastoma. Phase II clinical trials showed limited clinical efficacy, when these compounds were evaluated alone or in combination either with bevacizumab, TMZ and radiation or RTK inhibitor (14,26,53–56).

An inhibitor for PI3K/mTOR is being studied in a phase I trial. It is called **voxtalisib** and has exhibited a moderate inhibition of this pathway having a safe profile, with 68% of patients having stable disease (14,57).

The MAPK signalling pathway is also very interesting. About 3% of GBM patients have the oncogene BRAF V600E. **Vemurafenib**, a BRAF inhibitor has been investigated as a therapeutic tool and the results show potential (14,26,58–60). Another target being considered is **sorafenib**, a Raf multikinase inhibitor. Phase I/II studies have been done and have shown that alone or in association with TMZ, TMZ and radiation, **bevacizumab** or **temsirolimus** the inhibition of tumour activity has not been relevant (14,26,61–64)

- **Epidermal Growth Factor Receptor inhibitors (EGFR)**

EGFR is an essential signal of the receptor tyrosine kinase pathways and is amplified in nearly 40% of glioblastomas and overexpressed in over 60% of GBMs (14,19). Since its upregulation contributes to the oncogenesis, EGFR can be an important target for GBM therapy (13,19).

Therefore, it has been developed a first generation of EGFR inhibitors, **gefitinib** and **erlotinib**. They are currently being used for lung cancer with EGFR-mutated and its use has also been studied for GBM, but with poor results (14). A phase II clinical trial in recurrent GBM, treated with gefitinib, has revealed a PFS rate of 13% at 6 months and an OS of 10 months (65,66).

Further research with gefitinib as monotherapy or in combination has revealed a low efficacy when contrasted to the current treatments, due to an inconstant and inadequate inhibition of the EGFR pathway (13,19,67,68). Relatively to erlotinib, when alone as treatment, has poor activity in unselected GBM (69–71), but when in combination has a mild response (13,72,73).

Later, a second generation of EGFR inhibitors was developed: **afatinib**, **dacomitinib**, **neratinib**. Generally, the clinical trials conducted with afatinib and dacomitinib have disclosed a controllable safety profile but a short efficacy when treating the glioblastoma. For neratinib, studies are not available, but they are currently in recruiting phase (13,14,74–77).

**Lapatinib**, a dual inhibitor of EGFR and of human epidermal growth factor receptor 2 (HER2), is currently used as advanced or metastatic breast cancer therapy, yet, is also being investigated as a potential GBM treatment. Nonetheless, the phase I/II clinical trials have demonstrated a low activity in unselected patients when using lapatinib alone or combined with TMZ or pazopanib (an antiangiogenic agent) (13,14,78–81).

Another potential therapy is the use of **cetuximab**, a chimeric monoclonal antibody. Phase II clinical trials using cetuximab were conducted and reported a safe profile but weak activity for recurrent GBM. When assessing its activity with bevacizumab and irinotecan, the results were better, even though, not superior (13,14,82–84).

Furthermore, there is another related oncogenic, EGFR vIII that results from the deletion of exons 2-7 of EGFR. Almost 20% of GBMs harbour this variant oncogenic (26,85). An antibody drug conjugate (ADC), **depatuxizumab mafodotin** (previously **ABT-414**), is being investigated. It is composed of EGFR-directed monoclonal antibody, **depatuxizumab**, linked to the potent tubulin inhibitor, **monomethyl auristatin F** (26,86). The information provided by the phase I clinical studies has shown a 6 months PFS rate of 28.3% and a 6 months overall survival rate of 72.5%. Has also shown low toxicity, despite of the specific ocular toxicities, frequently, reversible blurred vision (65%) and dried eyes (29%). There is still the need of more studies, therefore, **depatuxizumab mafodotin** randomized phase II/III trials are ongoing (26,86,87). There is also a vaccine under development against this specific target, **rindopepimut**, that will be explained further in this thesis.

- **Platelet-Derived Growth Factor Receptor (PDGFR)**

PDGFR is another tyrosinase kinase receptor often overexpressed and altered in all types of glioblastoma (13,26). The activation of this pathway leads to tumour growth, and angiogenesis, making this receptor a target for glioblastoma therapy (13).

**Imatinib**, a kinase inhibitor of PDGFR, growth factor receptor (c-KIT) and, inhibitor of BCR-ABL, was studied in patients with glioblastoma (13,19). The results of the clinical trials conducted showed poor results: imatinib in monotherapy, presented a progression-free survival (PFS) of 16% at 6 months, in a phase II clinical trial with recurrent disease; (13,88–91) and, imatinib in addition with hydroxyurea, showed no relevant anti-tumour activity (13,92,93). Despite the poor chemotherapeutic results, imatinib improved the cytotoxic effect of radiotherapy in GBM cell lines (19,94).

CP-673,451, an inhibitor of PDGFR-β, is being studied in human tumour xenografts grown to test its efficacy against GBM.

Multi-kinase inhibitors were also studied. **Dasatinib**, multi-targeted RTK inhibitor (PDGFR, c-KIT, SRC and EPHA2), was investigated in a phase II clinical trial. The patients had recurrent GBM and their selection was made based on the overexpression of at least 2 dasatinib targets. Although it was made a meticulous selection, the results weren't as expected, as it failed to improve OS (13,14,26,95). **Nintedanib**, inhibitor of PDGFR α/β, FGFR and VEGF, has also

been unsuccessful on treating patients with recurrent GBM, even with prior bevacizumab treatment (13,14,96,97). **Sutinib**, multi-targeted RTK (PDGFR, VEGF, CD117, RET, CD114 and CD135) was also studied, in a phase II clinical trial. The results showed limited activity when administered alone, but further studies are necessary to search its potential activity when combined with alkylating agents (13,14,98).

- ***p53 Pathway***

p53 is a tumour suppressor protein that is essential to arrest cell-cycle and inducing apoptosis in damaged cells (14,26). This pathway is constituted of MDM2, MDM4 (negative regulators) and Tp53. When there are stressful conditions, such as DNA damage, p53 is activated through a cascade of phosphorylation events, and depending on the type of cellular stress, there is upregulation or repression of genes involving cell-cycle arrest, apoptosis and DNA repair. Cellular levels of p53 are controlled by its negative regulators, MDM2 and MDM4, either by degradation of p53 or by nuclear exportation (99).

This pathway is dysregulated in 86% of GBM cases and it is caused by direct gene (Tp53) mutation or deletion, or amplification of MDM2 or MDM4 (14,15,26,100).

Based on this, there are several experiments in development to create targeted therapies of this mechanism. There are some studies where they tried to reactivate the p53 pathway by using gene therapy with an adenovirus vector or pharmacological approaches. The phase I trial with the adenovirus showed poor results. As for the pharmacological approaches, the results were equally disappointing. It is believed they had a low potency and poor BBB penetration (14,26,100).

Although the previous results, there are other studies in development, targeting the MDM2. There is a phase I clinical trial ongoing that is expected to show promising results in the inhibition of this target and activation of the p53 pathway, stimulating antitumor activity, as the preclinical studies have shown in GBM models (14,26,100,101).

Since most of GBM cases have an alteration in this specific pathway, exploring these as potential therapeutic targets can be an advantage when treating this disease (26).

- ***Retinoblastoma protein (pRb) Pathway***

As mentioned before, the pRb pathway is disrupted in 79% of GBM cases (15).The pRb pathway is composed by cyclin-dependent kinases (CDKs) - CDK4, CDK6; inhibitors of the INK4 family, which is a family of cyclin-dependent kinase inhibitors (CKIs) of CDK4 and CDK6; D-type cyclins; CCND2 gene (encodes G1/S-specific cyclin-D2); CDKN2A/B gene (encodes p16 and p14ARF , members of INK4 family) and retinoblastoma protein 1 (Rb1). This signalling transduction pathway starts with D-type cyclines bonding with CDK4 or CDK6, becoming active complexes. Then, CDKs phosphorylate pRb which stops its activity, being regulated by external factors (14,102)

All the mentioned components of this pathway are potential targets in the therapy of glioblastoma (14). Considering this, pre-clinical trials were enrolled to inhibit CDK4/6 (oncogenes in a subset of GBM, essential to the growth and survival of the tumour) (103,104). Additionally, a Phase-2 clinical trial (NCT01227434) was conducted to evaluate the safety and efficacy of **palbociclib** (inhibitor of CDK4/6), given the previous pre-clinical data and the success in breast cancer therapy. The results were not pleasing, but it is believed that if patients are chosen considering the sequencing of Rb1 wildtype, and other pathway alterations, the results can give additional knowledge (105). Considering this, other clinical trials are under progress, exploring new results and new inhibitors of CDK4/6 such as **ribociclib** and **abemaciclib**, as they show promising efficacy (14,105).

- ***Others***
  - **Polyamine Biosynthetic Pathway**

Polyamine biosynthetic pathway is very important to the cells as it produces polyamines responsible for many cellular processes, namely, proliferation, development and growth. The components of this pathway are also important in the synthesis of amino acids and ribosome function.

DMFO is an irreversible inhibitor of ornithine decarboxylase, which is involved in polyamine synthesis, being a rate-limiting enzyme (3,158). DFMO reduces tumour cell proliferation and inhibits a pathway of CSCs (158). There is as in vitro study that has investigated the association treatment between DMFO, TMZ and radiation in three GBM cell types (U87G, U251MG and T98G). The combination increased cell death stablishing a prospect new therapy. For this to happen, this combination needs more studies, especially using in vivo models (3).

# Immunotherapy

Immunotherapy is known as therapy that inhibits a specific target but also stimulates the body's immune system to create an innate (antigenic-nonspecific) or adaptive immune response (antigenic specific) against this target (14). There are many forms of immunotherapy, such as: targeted antibodies, cancer vaccines, adoptive cell transfer, tumour-infecting viruses, checkpoint inhibitors, cytokines, and adjuvants.

- ***Adoptive cellular therapies (ACT)***

Adoptive cellular therapies are a branch in the immunotherapeutic sphere that has recently arisen. In this immunotherapeutic regimen, lymphocytes are taken from the patient, altered with the purpose of recognition of cancer cells and then infused back in the patient. Consequently, the lymphocytes can mark the tumour cells and neutralize them (106).

There are different types of adoptive cell therapy that include: chimeric antigen receptor T-cell (CAR T-cell) therapy, tumour-infiltrating lymphocyte (TIL) therapy, T cell receptor (TCR) T cell therapy.

- **CAR-T Cells Therapy**

CAR T cells stands for chimeric antigen receptor T cell therapy T cells are obtained from peripheral blood of patients and are genetically engineered to express a CAR molecule on the cell membrane. This receptor is specific for antigens of the tumour (14,106,107).

CAR T cells are currently being used in haematological malignancies, targeting the antigen expressed in B cells, CD19. Research is being made, regarding its use in glioblastoma. CAR T cells are being developed to target these GBM-specific antigens: Tyrosine Kinase-Type Cell Surface Receptor (HER2), Interleukin 13 receptor α 2 (IL-13Rα2) and EGFRvIII.

In 2010, a phase I clinical trial, with a total of 17 participants, was conducted targeting HER2. The median OS after the infusion was 11,1 months and after diagnosis was 24,5 months. HER2-CAR VSTs were detected for up to 12 months after the infusion (106,108). Further studies are being enrolled to improve the activity of HER2-CAR VST by augmenting their persistence (106,109) and function (106,110,111).

Infusion of CAR T cell in one patient with recurrent glioblastoma, targeting IL-13Rα2 revealed regression of the tumour with no side effects (22,112). Another trial, conducted in 3 patients with high grade glioma (HGG) showed similar results, with reduced expression of IL-13Rα2

(106,113). In an attempt to improve the outcomes, other clinical trials are being enrolled, with optimization of this target and the process of infusion (106,114).

CAR T cells against EGFRvIII mutation were also design and studied in a clinical trial. 10 patients with recurrent GBM were enrolled and attained safe and promising results. However, progression occurred in almost all cases and there are signs that tumours may adapt and escape these kinds of therapeutics (22,106,115). To supress this, a preclinical trial with immune-modulatory therapies is being conducted. With this adjuvant treatment, it is possible to stop the immunosuppression (106,116).

CAR T cells may be a helpful tool in treating glioblastoma, although there are some issues that must be overcome: antigen escape and tumour heterogeneity.

- **TIL Therapy**

TIL therapy stands for tumour-infiltrating lymphocyte therapy (106). The treatment with TIL's starts at the time of the resection of the tumour, where they collect these lymphocytes that are tumour-specific. Afterwards, they can isolate them or modify them genetically to recognize tumour mutations. Subsequentially, they are expanded and infused back in the patient (106,117,118). This therapy may have a future in treating glioblastoma, since it uses the patients T cells that already recognize the tumour as a treatment (106,117) .There are some issues that must be study carefully and overcome, such as the potential toxic effects and the risk of cytokine release syndrome (106,119).

- **TCR Therapy**

TCR therapy, stands for T cell receptor (TCR) T cell therapy, has revealed a successful outcome in metastatic melanoma. TCRs are usually expressed in T cells and they can specifically recognize and bind to antigens and after, induce apoptosis. The TCR therapy uses T cells attained from the patient's peripheral blood. To improve the antigen recognition, they are genetically modified to present tumour-specific α and β chains. Afterwards, T cells are expanded and introduce again into the patient (106,117,120–122).

TCR therapy has clinical application in treating metastatic melanoma, targeting the melanoma-associated antigen recognized by T cells (MART-1) and melanoma-associated antigen A3 (MAGE-A3), and, also in synovial sarcoma (106,123,124). Research is ongoing to access the use of TCR therapy also in high grade gliomas (HGG) and in GBM. (106,125)

## ▪ *Vaccine Therapy*

Cancer vaccines, like the regular vaccines, expose the immune system to an antigen present in the tumour. This first contact will stimulate the T cells, and trigger an inflammatory response addressing the tumour. This initial encounter will build an immune memory for upcoming contact (106,126).

- **Dendritic Cell Vaccines**

DCVax, a dendritic cell (DC) based cancer vaccine, uses autologous tumour lysates or tumour antigens to cause an immune response. Nowadays is approved in Switzerland for treatment of Glioblastoma (13,22,127).

The vaccine is made upon extraction of blood from the patient, with isolation of monocytes that will posteriorly differentiate into dendritic cells. Afterwards, autologous tumour lysates or antigens are cultured with the DCs for posterior recognition of the cancer cells. Finally, the formed vaccine is injected into the patient (106).

Preclinical studies using mouse models have confirmed a good response in the CNS (128,129). Further clinical trials have been done to verify the immune response. In 2 Phase I

clinical trials in patients with newly diagnosed glioblastoma and with recurrent GBM, the results obtained showed a good prognosis, achieving respectively, an OS of 9.6 months (with 2-year OS of 14,8%) and a median OS of 24 months (13,130,131). In a Phase III clinical trial, the results were even more encouraging. The trial was conducted in patients with newly diagnosed GBM and attained, for patients with methylated MGMT (n = 131 of 331), mOS of 34.7 months from surgery, with a 3-year survival of 46.4% (13,132,133) The DCVax has a safe profile and a suggested great efficacy. Although the substantial effectiveness, it is required more studies to evidence these results.

In additional research, it is being investigated the combination of DCVax with standard therapy (22,134), with immunomodulatory therapies, as for example, pre-conditioning with potent recall antigen (such as tetanus/diphtheria toxoid) (22,106,135) and in combination with toll-like receptor agonists (22,136). In general, the results show that the combinations are safe and feasible.

- **Peptide Vaccines**

Peptide vaccines are made from tumour associated antigens. Since they are made from tumour antigens, they are not specific to one patient, having a broad range.

As mentioned before, **rindopepimut** is a peptide vaccine targeting the mutated receptor, EGFRvIII. Early phase clinical trials have demonstrated an improvement on overall survival, whether using the vaccine alone or in combination with TMZ (137–139). However, new studies have shown no survival advantage (13,106,140,141).

Another peptide vaccine that targets the tumour antigen HLA-restricted Wilms tumour 1 (WT1) is also being examined in patients with recurrent glioblastoma and with newly diagnosed GBM (in combination with standard treatment). The results were promising as it has shown clinical activity (13,14,142–144).

**SurVaxM** is another peptide vaccine under development, marking survivin, an anti-apoptotic protein responsible for cancer cells survival, being expressed in 95% of GBM cases. A phase I clinical trial was conducted and the results are promising, with a safe profile an OS of 86.6 weeks, with an increase of 56 weeks, when compared to therapy with chemotherapeutic agents (1,145).

- **Heat Shock Protein Vaccination**

Heat Shock proteins (HSPs) are produced when the cells are exposed to stressful circumstances. They stimulate the immune system, activating both innate and adaptive immune systems, and induce an anti-tumour immune response, by bonding to antigens and deliver them to antigen presenting cells (APC). Since the tumour cells have an increased expression of HSPs, these proteins make a useful instrument in cancer vaccine development to fight glioblastoma (22,106).

The development of the vaccine follows 4 stages: resection of glioblastoma; release of HSPs, that primarily, connect to the tumour antigens, isolation and purification of these complexes (HSPs-tumour antigens) to make the vaccine and administration to the patient. Once administer, the HSPs-tumour antigen complexes are delivered to APCs, that presents them to major histocompatibility complex (MHC) class I molecules for recognition of Cytotoxic T lymphocytes (CTLs). CTLs then cross BBB and mark GBM cells, resulting in the anti-tumour response (106).

HSP peptide complex-96 (HSPPC-96) is being studied as a patient specific vaccine (**Prophage**) against glioblastoma. The phase II clinical trial conducted, showed promising results due to a safe profile and significant immune response to the treatment. This study also

showed that pre-treatment of lymphopenia may diminish the efficacy of the vaccine. In a subsequent phase II clinical trial, it was investigated the use of this vaccine in combination with TMZ, and the results ensure the security and effectiveness when using both (22,106,146). More studies are currently on going, exploring new populations (paediatric population) and new combinations (for example, using pembrolizumab, an anti-PD-1 checkpoint inhibitor) (106).

- ***Checkpoint Inhibition***

Immune checkpoints are an important tool in immune regulation to avoid autoimmunity. They are expressed in many cells, like T effector cells, APCs and myeloid-derived cells. Checkpoint inhibition, in contrast, is the treatment that targets immune checkpoints to block them, in order to restore the normal immune system function (106).

Many studies are being made to verify the possibility of using checkpoint inhibitors as glioblastoma therapy. Although the results published so far don't present the promising results expected, there is still expectations of them being used in GBM treatment.

A phase III clinical trial using **nivolumab**, an anti-programmed cell death-1 (PD-1) monoclonal antibody, showed no benefit in the OS. However, a small subset of patients improved their OS to 11 months, better that therapy with bevacizumab, which reaches an OS of 5.3 months. Additional analysis in this group is necessary to understand the differences in this population (immune status, tumour biomarkers) that led to this outcome (106,147).

Another checkpoint inhibitor being studied is anti-Lymphocyte-activation gene 3 (LAG3) monoclonal antibody, named **LAG525**.However, the results haven't been released yet.

## Virotherapy

Virotherapy uses virus as therapeutic agents and comprises: oncolytic virotherapy, viral vectors for gene therapy and viral immunotherapy.

Oncolytic virotherapy is based on the ability of using replicated virus, attenuated or genetically modified viruses to target specifically the cancer cells, inducing cell death through different mechanisms. Some of these virus are also immunogenic, meaning that they have the capacity to generate an immune response (106,148).

Many viruses are being studied as potential glioblastoma therapy.

A therapeutic approach with **ParvOryx01**, a H-1PV oncolytic virus, is being developed. A phase I/II 2a clinical trial was conducted on GBM and the results were promising, as ParvOryx01 seemed to improve survival and stimulated the immune system with an antitumor effect (1,149).

**PVSRIPO**, the recombinant polio-rhinovirus chimera, binds to the receptor CD155 found in several neoplastic cells. Preclinical studies of treatment with PVSRIPO, in murine models with breast and prostate cancer and preclinical studies in athymic mice bearing the conventional subcutaneous (s.c.) or intracerebral glioma xenografts have shown promising results, as the tumour infection and the innate response provoked by the virus leaded to the regression of the tumours (106,150,151). A phase I clinical trial was conducted in 61 patients and concordantly with the previous results, revealed an improved overall survival with 21% of patients surviving between 24 and 36 months (106,152).

Preclinical studies and phase I clinical trial were held with **DNX-2401** (**Delta-24-RGD**) against high-grade glioma. This virus is an oncolytic adenovirus whose infection causes oncolytic

effects and anti-glioma immunity, resulting in the increasing of long-term survival (106,153,154).

Zika Virus is also being studied. In vitro and in vivo studies were made, and the results were encouraging as zika virus has oncolytic activity against GBM stem cells. Additional research is needed to verify this results (106,155,156).

It is also being investigated the possibility of using virotherapy in combination with chemotherapy or radiotherapy. Preclinical trials tested the use of the virus Herpes-Simplex increase of delivery of the virus to the tumour cells, and damage on the splitting cells. Further studies are needed to confirm the efficacy of these treatments (106,157,158).

## Gene Therapy

Gene therapy, an experimental technique still under study, stands for the introduction, substitution or inactivation of genes in order to treat an illness.

In the specific case of glioblastoma, there are some preclinical and clinical researches on going, but there aren't many published results. These researches are exploring several strategies for achieving the modification in genes, such as: insertion of drug sensitivity genes, suicide gene therapy (using HSV thymidine kinase), transfer of wildtype p53 or p27, among others (22)

A phase III clinical trial of herpes simplex virus, thymidine kinase and ganciclovir as gene therapy for GBM hasn't shown promising results (22).

In another clinical research, testing a retroviral replicating vector (RRV) - Toca 511, the results shown are promising. This phase I clinical trial on a patient with glioblastoma has shown favourable safety profile and a better OS than lomustine alone (1).

## Other Potential Therapies

- ***Cholesterol Metabolism***

The brain has 20% of the total cholesterol of the human body. This cholesterol is synthetized in the brain, since the BBB is impermeable to it. The synthesis of cholesterol is of big importance to the development of the cancer meaning it is a possible therapy target. More studies are needed but there is an evidence linking the metabolism of cholesterol and the development of brain tumours, specifically glioblastoma (15).

- ***Hyperthermia***

Hyperthermia is a therapy based only on the elevation of the temperature at the tumour location (to 41-46ºC) to damage the cancer cells. There are several types of mechanisms to induce hyperthermia, such as: microwaves, ultrasound, radiation, magnetic nanoparticles and thermal conduction. These techniques are under study, but in general the results are promising. These therapies have demonstrated the capacity of being used in monotherapy or in combination, the ability of altering the BBB, which allows for chemotherapeutic agents to reach the tumour and an absence of adverse reactions (1,22).

# Conclusion

Glioblastoma is a complex tumour with a bad prognosis. There are many new treatments under development trying to control and/or reverse this outcome. Many of these new therapies have drawbacks due to many reasons: some related to the brain, an elaborate environment, that has many barriers such as the BBB; some related to the tumour, a heterogenous cancer, with many mutations in the cell pathways, and some to the therapy itself, as for example the CAR-T cells that has a lack of long-term response. The key to resolve these issues starts with a better clinical trial design, molecular screening of the patients to better address the treatments.

However, with the constant gained knowledge in the scientific field and the endless development of the technologies, the future for glioblastoma therapy is promising. The evolution of the glioblastoma standard therapies, with improvements in the surgical and imaging methods, with the creation of new ways to deliver the chemotherapeutic agents and the turning of radiation therapy into a more focalized therapy to the tumour site, are signs of these advances.

Further progress is being made with innovative therapies. The vaccines, SurVax, Prophage and DCVax; the virotherapy, with ParvOryx01, PVSRIPO; the CAR-T Cells therapy, Vemurafenib, depatuxizumab mafodotin had encouraging results that conducted to a tumour regression and increasing of long-term survival, Sonolisib, Voxtalisib leaded to a stable disease in most of the patients and other molecules, such as erlotinib showed a moderate response, but in combination with other treatments its action was potentiated.

Many of these innovative therapies are still being studied either alone or in combination with the current therapies and the novel ones.

Since the future of Medicine lays on personalized treatments, the key to successful therapies for GBM will stand for the same principle and will possibly combine the referred treatments.

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